Journal Lancet
Lancet Publications, [illegible]
Northwestern Pediatric Society
8th South 10th Street
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VOLUME XII *June 1956* NUMBER 6

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OF THE CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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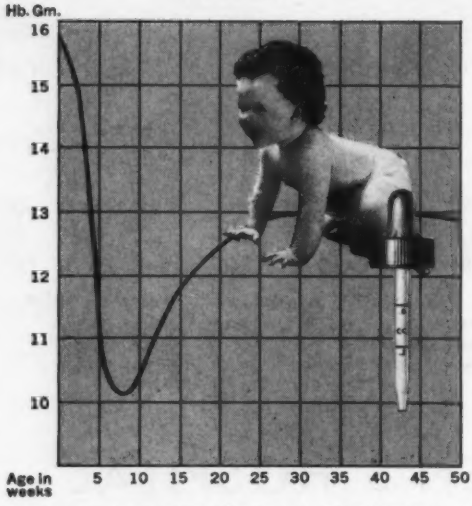
to help you combat iron deficiency in infants...

How Fer-in-Sol improved infants' blood pictures



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(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86: 553, 1954. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 155, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 275, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

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Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinicopathological conferences and from the monthly Staff meeting.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $2.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D.C. Please notify on change of address.

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Entered as second class matter November 21, 1946 at the post office at Washington, D.C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

EPIDERMOLYSIS BULLOSA

Enid F. Gilbert, M.D.

Epidermolysis bullosa is a disease characterized by the spontaneous development of bullous and vesicular lesions of the skin. The disease was first described by Von Hebra[1] in 1870. It was not until 1935 that Herlitz[2] first reported the lethal form of the disease, of which the following case is an example.

CASE D. M. NUMBER 55-9403

This colored female infant was born at the D. C. General Hospital on August 8, 1955, following a normal, full-term pregnancy and spontaneous delivery. The birth weight was 6 pounds 4 ounces. Within the first two hours after birth, clear bullous lesions appeared over the trunk and extremities. These bullae later ruptured, leaving large red denuded areas. The infant was admitted to Children's Hospital at six days of age.

The family history revealed that both parents were living and well, with no known hereditary diseases in either family. There was no consanguinity.

The physical examination on admission revealed a fairly well developed and well-nourished colored female infant. The temperature was 99.4°(F); the pulse rate, 120 per minute; and the respiratory rate, 30 per minute. The weight was 6 pounds, 2 ounces. There were bullous lesions, as well as denuded, red raw areas on the face, trunk, and all extremities. The extremities showed some resistance to passive movement, and the joints were held in flexion. There were no visible lesions of the mucous membranes, and the finger and toe nails showed no dystrophic changes. The rest of the physical examination was essentially normal. The hemoglobin was 15.0 grams per 100 ml.; hematocrit, 52 per cent; leukocytes, 9,700 per cubic millimeter; segmented cells, 12 per cent; lymphocytes, 39 per cent; monocytes, 38 per cent; basophils, 7 per cent; and eosinophils, 4 per cent. The platelets were adequate and the sickling preparation and the serological test for syphilis were negative. The total serum proteins were 7.0 grams per 100 ml.; the albumin, 3.8 grams per 100 ml.; and globulin, 3.2 grams per 100 ml.

On admission the infant was placed in an Armstrong incubator. Local therapy consisted of daily baths in 1:8,000 potassium permanganate solution. Erythromycin was given in a dosage of 100 mg. daily. A culture obtained from an unruptured bullous lesion grew a small colony of *E. coli* organisms. This, however, was considered to be a contaminant. A skin biopsy was obtained on August 22, 1955, and the microscopic appearance was consistent with epidermolysis bullosa. The infant's condition gradually deteriorated, and on September 8, 1955 at one month of age, she died.

At postmortem examination, the skin was generally dry with widespread and irregularly shaped yellowish-red ulcerative areas, as well as some fresh bullous lesions. These lesions involved almost the entire skin surface (Figure 1). The oral mucosa revealed small grayish-white ulcerative lesions. There was generalized lymphadenopathy. There was no atrophy of the nails. The parenchymatous organs were unremarkable. Microscopic examination of material obtained from multiple areas of the skin showed separation of the corium from the overlying epidermis, edema of the elastic tissue and acute and chronic inflammatory cell infiltration (Figure 2). No in-

FIG. 1. Appearance of the infant at three weeks of age showing widespread denudation of the epidermis subsequent to rupture of bullous lesions.

clusion bodies were seen. There was an interstitial pneumonitis, and fatty metamorphosis of the liver.

Bacterial culture of the skin lesions and the lungs grew *Micrococcus pyogenes, variety aureus*, coagulase positive; non-hemolytic streptococci; and *E. coli*. The heart's blood culture grew *E. coli* and *Proteus* organisms.

DISCUSSION

The *etiology* of epidermolysis bullosa is obscure. Several theories have been advanced including endocrinological disturbance, cutaneous, vascular, and neurovascular anomalies, but none has been universally accepted. Heredity plays an important role, and consanguinity of the parents may predispose to the condition. The lesions are usually present from birth. There are three forms of the disease:

FIG. 2. Microscopic appearance of the skin showing separation of the epidermis from the corium.

1) *Epidermolysis bullosa simplex* is usually inherited as a mendelian dominant, and is characterized by the formation of bullous lesions which heal promptly without scar formation. The mucous membranes are rarely affected, and the disease either improves or subsides at puberty.

2) *Epidermolysis bullosa dystrophica* is usually inherited as a mendelian dominant. The lesions heal, leaving atrophic scars which persist throughout life. Dystrophic changes in the nails as well as lesions of the mucous membranes may be associated with this dystrophic form.

3) *Epidermolysis bullosa hereditaria lethalis* is usually inherited as a mendelian recessive. Bullous lesions are present at birth or shortly thereafter, and death usually occurs within three months. Oral lesions as well as dystrophic changes of the nails are usually present.

Histopathology: Separation and vesicle formation in the superficial layers of the skin occur in all cases. The bullae are always subepidermal in location in the dystrophic and lethalis forms. In the simplex form they may be found in a subepidermal, intraepidermal or subcorneal location.[3] Edema of the skin is present and acute inflammatory cells are seen if secondary infection has occurred. Small numbers of eosinophils may be seen in the lesions. Absence or diminution of elastic tissue in the papillary and subpapillary layers has been noted by some observers.[4, 5, 6] This change in the elastic tissue may, however, be secondary to inflammatory reaction, and is not a consistent finding.

The *differential diagnosis* of bullous lesions in the neonatal period includes a great number of conditions,[7] the commonest being congenital syphilis, exfoliative dermatitis (Ritter's disease), pemphigus neonatorum, and bullous impetigo. The bullae of congenital syphilis occur on the palms and soles, and bullae contain turbid or purulent fluid. Serological tests for syphilis are positive. Exfoliative dermatitis usually begins as a hyperemia with the later development of vesicles containing purulent fluid. Fluid from unruptured vesicular lesions of pemphigus neonatorum and bullous impetigo likewise is purulent, and culture reveals staphylococcal or streptococcal organisms. Congenital porphyria may produce bullous lesions with resulting pigmented scars; however, the presence of porphyrins in the urine and a family history of the disease will help confirm this diagnosis.

The *treatment* of the disease is symptomatic. Prevention of trauma to the skin is important in the simple and dystrophic forms. Appropriate antibiotics should be used in the presence of infection. Steroid therapy appears to be ineffective[8] and introduces the hazard of disseminating infection. Replacement of serum proteins and blood may be necessary. The prognosis is good in all but the lethalis form.

SUMMARY

1. A case of epidermolysis bullosa hereditaria lethalis is reported, death occurring at one month of age.

2. Three types of the disease exist. The simplex and dystrophic forms are inherited as mendelian dominants and are benign conditions. The rarest and most severe, the lethalis form, is inherited as a mendelian recessive.

3. The differential diagnosis and histopathology are discussed.

4. No treatment has thus far been effective in this disease.

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Acknowledgement. The helpful assistance of Dr. Kinsuke Nishimura with the photography and post mortem examination was appreciated.

MECONIUM ILEUS

SUNDAY CONFERENCE CASE

Joseph M. LoPresti, M.D.

The relationship between meconium ileus and cystic fibrosis of the pancreas has become evident. The following report illustrates this relationship and considers some of the factors involved in pathogenesis, diagnosis, and treatment of fibrocystic disease in general and meconium ileus in particular.

CASE REPORT

This white girl was born at D. C. General Hospital on September 3, 1955, and was admitted at five days of age to Children's Hospital, with the chief complaint of persistent vomiting. The pregnancy was uneventful, and delivery was normal and spontaneous. The baby's birth weight was 5 pounds, 11 ounces. Breast feeding was begun soon after birth, but the infant vomited after each feeding and spit up mucus between feedings. On the day prior to admission she vomited green bile.

Family history disclosed that 2 siblings (5 and 7 years old) are healthy. One sibling died in June 1954, at the age of 3 days, after an operation for intestinal obstruction.

On admission the baby had a moderate degree of jaundice and a distended abdomen. Gastro-intestinal x-rays showed a marked distention of the small bowel and a barium enema revealed the rectum and the sigmoid to be narrow with an average diameter of 0.5 cm. The barium could not be propelled beyond the distal descending colon. Results of a blood count were: Hemoglobin 14.2 grams, white blood cell count 5,500 with 20 per cent segmented forms, 6 per cent bands, 63 per cent lymphocytes, 8 per cent monocytes, and 3 per cent eosinophils.

On the day of admission a laparotomy was performed, and meconium was found obstructing the terminal ileum. After the involved segment of ileum was resected, an end to end anastomosis was performed. Following the operation the baby became more jaundiced and distended. After three days a large dark green stool was passed. The baby's condition became worse and on September 11, respiratory distress developed and she died 24 hours later at 10 days of age.

Autopsy Findings

At autopsy the body was that of a well developed 10 day old white female infant weighing 2.8 kilograms. There was slight icterus of the skin and mucous membranes and moderate abdominal distension. A 7 cm. linear incision in the right rectus region was closed with black silk sutures.

When the thoracic cavity was opened, both lungs were noted to be congested and edematous; the heart and great vessels were not abnormal.

As the abdominal cavity was being opened, markedly dilated loops of dark brownish ileum bulged through the incision. The serosal surface of the intestine was studded with patches of friable green exudate and the loops of small intestine were adherent. The colon was collapsed, the diameter averaging 0.7 cm.; its entire lumen was patent.

The surface of the liver was covered with strands of greenish friable exudate. The mucosa of the stomach, duodenum and jejunum showed numerous petechiae. The mucosa of the ileum was congested and was filled with thick, tenacious, dark greenish black meconium. There was an end to end anastomosis of the ileum one centimeter from the ileocecal valve. The edges were approximated with black silk sutures; a 0.3 cm. opening in the suture line communicated with the peritoneal cavity. Both cerebral hemispheres of the brain showed marked congestion. The remainder of the organs were grossly unremarkable.

On microscopic examination the lungs showed areas of hemorrhage, emphysema, atelectasis and edema as well as patchy areas of bronchopneumonia. There was dilatation of the pulmonary, bronchial and tracheal mucous glands which were distended with acidophilic material. The architecture of the liver was distorted because of widespread focal increase in fibrous tissue, multiplication of bile ducts, and infiltration with acute and chronic inflammatory cells. Many bile canaliculi were distended with bile, and the Kupffer cells contained bile stained material.

Sections from all areas of the pancreas showed a moderate increase in interlobular fibrous tissue. The alveoli and ducts were distended with acidophilic material, the individual alveolar cells containing a large number of acidophilic granules. The mucous glands of the submucosa of the esophagus were distended with acidophilic

material. The serosa and muscle layers of the small intestine were infiltrated with acute and chronic inflammatory cells, especially in the region of the surgical repair. The mucosal epithelium of both small and large intestines showed focal necrosis. The remainder of the organs were unremarkable.

Final Pathological Diagnosis

1. Meconium ileus
2. Peritonitis
3. Status post operative end to end ileal anastomosis
4. Pulmonary hemorrhage, emphysema, atelectasis, and edema
5. Bronchopneumonia

DISCUSSION

Dr. LoPresti:

In the time allotted, it would be impossible to discuss all of the aspects of cystic fibrosis of the pancreas. I think, however, that all of us can benefit from an historical review of this interesting disease. The first pathological description was made by Landsteiner in 1905.[1] Interestingly enough, he reported the changes in the pancreas of a patient who had died of meconium ileus, similar to the patient reported today. In 1919, Passini[2] differentiated fibrocystic disease from celiac disease which it superficially resembles in its clinical manifestations. It was not until 1932 that Siwe[3] confirmed the clinical impression by an actual analysis of the duodenal juice. In 1938, Andersen[4] demonstrated the variable nature of this disease process. She divided these patients into three large clinical categories. The first included infants born with clinical disease of which meconium ileus is an illustration. The second is the most common and included those patients who died before 6 months of age either of respiratory disease or as a result of nutritional failure. The third group included those patients who lived for a varying period beyond 6 months of age, and in whom gastrointestinal symptoms were minimal, but who ultimately died of respiratory infection. Andersen laid down the basis for the dietary management when she demonstrated the altered physiology which results from pancreatic insufficiency. In 1944, Farber[5] reported in detail the histopathological findings and for the first time demonstrated the systemic nature of this disease entity. He showed that the same pathological changes which occur in the pancreas may also be found in the gastrointestinal tract, lungs, liver, gall bladder, and biliary tree. He also found these changes in the salivary glands and stated that the name, "fibrocystic disease of the pancreas" was misleading. He suggested the term "mucoviscidosis" which at the present time also appears to be a misnomer. Schwachman[6] in 1951 reported a series of patients whose duodenal juice had normal tryptic activity, and whose clinical features were respiratory almost exclusively. The viscosity of the

duodenal juice was elevated. He found, however, that the duodenal juice of patients showed diminished or absent tryptic activity after varying periods of time. Bodian[7] showed for the first time the familial nature and genetic transmission of fibrocystic disease. He also demonstrated that all of the salivary glands with the exception of the parotid are involved and suggested the term "mucosis" since the mucus secreting glands throughout the body are involved. During this period Kessler and Andersen[8] illustrated the inability of patients with fibrocystic disease to tolerate elevated external environmental temperatures. At that time the reason that these patients were unduly susceptible to heat prostration was obscure. It had long been known that if they were moved to a hot, dry climate in an attempt to minimize respiratory infections, they did poorly. In 1953, di Sant'Agnese and his group[9] showed that the tendency toward heat prostration was caused by an abnormal sweat mechanism. The sweat of patients with fibrocystic disease contains an increased amount of sodium chloride. Since then others[10, 11, 12] have demonstrated this finding not only in patients with the disease but also in members of the same family who possess no clinical manifestations. More recently, Bessman[13] reported that the parotid saliva of these patients also contains an abnormally high amount of sodium chloride. At the present time, 99 per cent of the patients examined have shown an increased amount of sodium and chloride in their sweat. This feature has not been demonstrated in any other disease. Whether this holds true for parotid saliva has not as yet been proven. Schwachman[10] has devised a method for collecting sweat which is simple and practical.

Bodian[6] in his excellent monograph established the concept that meconium ileus is a manifestation of fibrocystic disease. There are many facts which support this view. For example, it was not until 1948 that the first successful operation for meconium ileus was performed; but if patients live long enough following successful relief of the intestinal obstruction, they develop the typical clinical features of fibrocystic disease. Too, there is a high familial incidence of fibrocystic disease in siblings of infants who are born with meconium ileus. I believe that the patient presented today illustrates this familial tendency. A previously born infant died as a result of congenital intestinal obstruction at another hospital. Finally, in patients who die because of a meconium ileus the same histopathological features are found as are present in older patients with fibrocystic disease. I would stress that this is a very variable disease and that the clinical features depend on the degree of pathological changes which are present in one or the other different organs.

Abnormal meconium is an example of an altered physiology resulting in intestinal obstruction, but chemically abnormal meconium associated with

fibrocystic disease is probably the commonest cause of congenital intestinal obstruction. Abnormal meconium may exist in conditions other than fibrocystic disease. For example, a physiological meconium plug may occur. Patients with this condition will develop abdominal distension and vomiting, but as gas pressure builds up proximally, the plug usually will pass spontaneously. If it does not, then digital stimulation or a saline irrigation will cause the passage of a large meconium plug which may be a cast of the entire large intestine. In intestinal atresia, the meconium proximal to the obstruction will become impacted. A similar finding may be present in volvulus of the newborn. There is one complication of abnormal meconium which it would be well to point out at this time, that of meconium peritonitis. This most serious complication results from perforation of the bowel and the subsequent escape of meconium into the peritoneal cavity. This results in a sterile, plastic peritonitis. When an x-ray is taken of the abdomen of such a patient in the supine position, the finding of intraperitoneal calcifications is pathognomonic of meconium peritonitis. While meconium ileus is the commonest cause of such a sequence of events, any intrauterine perforation of the intestinal tract can produce a meconium peritonitis.

The clinical features are clearcut in meconium ileus. They are the symptoms of congenital intestinal obstruction such as abdominal distension, vomiting, and the failure to pass meconium. An astute observer may note a rather thick, purulent, viscid nasal discharge which may suggest the diagnosis. I will stress that patients with a congenital intestinal obstruction may pass a few small meconium stools which will do nothing more than stain the diaper. This may mislead one into believing that an organic obstruction is not present. The roentgenographic features of meconium ileus are those which indicate a low, small bowel obstruction. In most instances the radiologist will only make the diagnosis of a congenital intestinal obstruction. However, on occasion it is possible to visualize fecal shadows or opaque shadows containing gas bubbles which may further suggest the diagnosis of meconium ileus. The presence of fibrocystic disease in siblings or the family history of other infants who have died of congenital obstruction adds weight to the diagnosis of meconium ileus.

The combination of volvulus and meconium ileus has been described. When this association occurs, the volvulus is secondary to the meconium ileus. The attempts of the obstructed bowel to dislodge the abnormal meconium results in a twisting of the small intestine. The combination of biliary atresia and meconium ileus is also a matter of record. The biliary atresia is secondary to the production of abnormal mucus which becomes inspissated and which stimulates fibrous proliferation and thus obliterates the biliary ducts. As a matter of fact, the pancreatic duct in many patients

with fibrocystic disease will also have a very small lumen for the same reason.

The immediate treatment of meconium ileus is surgical. However, once the intestinal obstruction has been relieved, the patient still presents the problem of fibrocystic disease with pancreatic insufficiency and involvement of the respiratory tract. Medical management has two goals: the prevention of nutritional failure and the control of respiratory infections. These patients need a high caloric intake, at least 20 to 40 per cent more than normal. The protein intake should be two to three times the average daily requirement. The addition of fat to the diet of a patient who has pancreatic insufficiency increases the caloric and protein losses. Therefore, dietary fat should be limited. The addition of pancreatic supplements is of doubtful efficacy, but probably no harm will occur from their use. In addition, these patients have difficulty in absorbing fat soluble vitamins. If untreated, they will show some clinical evidences of Vitamin A deficiency. It follows that a large daily intake of Vitamin A is essential to proper therapy. If these dietary measures are instituted early, the nutritional failure which is so typical of the chonic cases will be aborted or minimized. The control of respiratory infections is of paramount importance in fibrocystic disease. Every attempt should be made to prevent the inordinate exposure of these patients to respiratory infections. The use of prophylactic antibiotics probably is worthwhile; but, most important of all, at the first sign of respiratory infection adequate therapeutic doses of antibiotics should be started immediately. Of therapeutic interest is the fact that in the majority of instances, the etiologic agent will be a *Staphylococcus aureus*. Therefore, the drugs of choice are those which are most effective in controlling staphylococcic infections. Many strains of staphylococci are resistant to penicillin. Chlortetracycline, oxytetracycline, tetracycline, chloramphenicol, and erythromycin are frequently effective antistaphylococcic agents. Therefore, I would suggest their use in the management of respiratory infections in these patients.

In conclusion, di Sant'Agnese[12] has discussed the problems in the diagnosis of fibrocystic disease. The typical patient with a characteristic history presents no difficulty. A number of features require some elaboration. First of all, the stool trypsin is the most unreliable test and for practical purposes should be discarded. False positive results may be obtained from the action of proteolytic bacteria in the intestinal tract. In addition, as little as one unit of trypsin in the stool will yield a positive test. Secondly, the analysis of the duodenal juice for its tryptic activity will yield definite results in about three-fourths of the patients. Approximately 70 per cent will demonstrate a decreased or absent trypsin. In other words, 30 per cent of patients with fibrocystic disease will have a normal trypsin content in their duodenal juice. Finally, since 99 per cent of the patients with fibrocystic disease

possess an increased amount of sodium chloride in their sweat, it follows that this is the most accurate and reliable laboratory test available at the present time. A number of patients with fibrocystic disease will show chronic bronchopneumonia, emphysema, and scattered areas of atelectasis. In this group there will be no gastrointestinal symptoms. Second to tuberculosis, fibrocystic disease is the commonest cause of this clinical triad. At the present time the only possible way to establish the diagnosis in this group of patients is by an analysis of the sweat for its sodium and chloride content.

In the past two decades important strides have been made in the diagnosis and treatment of fibrocystic disease of the pancreas. A more nearly complete comprehension of the disease is now possible. However, there remains much to be accomplished. An exact etiology is yet to be determined. In addition, although antibiotics and diet have lengthened the life expectancy of these patients, the ultimate prognosis remains poor.

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CLINICAL PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D., Enid F. Gilbert, M.D.
Discussed by: Joseph M. LoPresti, M.D.

PROTOCOL

This 15 month old colored girl was well until the morning of admission when her mother noticed that the baby was listless and vomited some poorly chewed peanuts. She also passed some undigested peanuts from the rectum. There had been no diarrhea, and no other symptoms were present.

The child was the product of a normal full term, spontaneous delivery. Birth weight was 8 lbs. 5 ozs. Feeding history and growth and development had been normal. The mother and father and four siblings were all living and well.

When examined in the Out Patient Department she was moderately dehydrated and very lethargic. Heart rate was 160 per minute, respiratory rate 18 per minute, and temperature 102. The ears, nose and throat were normal. There were no cardiac enlargement or heart murmurs. The lung fields were clear and the abdomen was soft. There was some nuchal rigidity and a positive Brudzinski sign. The reflexes were hypoactive.

Laboratory data were as follows: Hemoglobin 6 gms per 100 ml, WBC 41,650 per cu mm, segmented forms 51 per cent, bands 49 per cent; two or three nucleated red cells were seen in every field and the erythrocytes were markedly hypochromic and showed marked anisocytosis and poikilocytosis. CO_2 was 31 vol. per cent. A lumbar puncture revealed a clear cerebro-spinal fluid containing 23 mg. of protein and 95 mg. of sugar per 100 ml and three white cells per cubic millimeter.

The child was admitted to the ward where a venous cut-down was begun. The infant failed to respond to the needle pricks during this procedure. Before any intravenous fluids could be given, the infant died. Intracardiac adrenalin was given to no avail. Death occurred 2½ hours after admission.

DISCUSSION

Dr. LoPresti:

There is, perhaps, no more distressing castastrophe to parents and physicians alike than to have an apparently normal infant die suddenly and unexpectedly. The problem presented in this protocol may be approached in one of two ways:

1. We can review the causes of sudden death in childhood and attempt to fit the patient into one or more of the numerous etiologies, or
2. We can analyze the patient's history, physical, and laboratory findings and arrive at conclusions which will ultimately lead us to a logical diagnosis.

In a case of sudden death, a good portion of the reasoning must, of necessity be speculative; but despite this handicap, logical deductions should produce some valid results.

In approaching this problem from an analysis of the etiologies of sudden death in childhood, I arrived at the conclusion that such an investigation was unrewarding. However, it affords me the opportunity of discussing the differential diagnosis of sudden death. In 1940, Rabson[1] analyzed 2,030 cases of sudden death in New York City. In the group between birth and 4 years of age, he found that sudden death was four times more common in males than in females. This sex difference has no adequate explanation. In almost 80 per cent death was due to disease of the respiratory tract. The causes include:

1. Respiratory system (pneumonia, laryngotracheobronchitis, atelectasis, diphtheria, asphyxia): 10 per cent.
2. Cardiovascular system (congenital heart disease): 10 per cent.
3. Digestive system (Malnutrition, diarrhea): 8 per cent.
4. Nervous system (hemorrhage, brain tumor, brain abscess, congenital aneurysm): 4 per cent.
5. Miscellaneous: 3 per cent.

Orr and Preisser[2] in a review of 188 sudden deaths at the Children's Hospital of the District of Columbia found that about 20 per cent occurred in the operating room. Other causes included:

1. Respiratory system: 18 per cent.
2. Prematurity: 15 per cent.
3. Infections (septicemia, Waterhouse-Friderichsen syndrome, meningitis): 15 per cent.
4. Trauma and burns: 9 per cent.
5. Congenital heart disease: 6.5 per cent.
6. Diarrhea: 3.5 per cent.
7. Miscellaneous: 13 per cent.

I feel that our patient will fall into the rarer, heterogenous, miscellaneous causes of sudden death. Therefore, the second approach of an analysis of the clinical features should prove to be more fruitful.

In summary the protocol describes a 15 month old colored girl whose short illness was characterized by listlessness, vomiting, dehydration, lethargy, fever, tachycardia, nuchal rigidity, a positive Brudzinski sign, hypoactive reflexes, anemia, leukocytosis, mild acidosis, normal spinal fluid, and death within 2½ hours after admission. I would dismiss the history of eating peanuts. It is difficult to conceive how the aspiration of a peanut could cause sudden death unless it produced asphyxia. There is no evidence to indicate that such a tragic accident occurred. In the differential diagnosis one must include:

1. The nervous system.
2. The respiratory system.
3. The cardiovascular system.
4. Severe infections.
5. The digestive system.
6. The blood and blood forming organs.

1. The nervous system: At first glance this would appear to be the most likely possibility. The neurological symptoms dominate and, indeed, obscure what may prove to be the most important features of the illness. Intraventricular and subarachnoid hemorrhage, rupture of a congenital aneurysm, and meningitis are excluded by the finding of a normal spinal fluid. Brain abscess and sinus thrombosis are preceded or accompanied usually by a focus in the respiratory tract. The examination of the ears, nose, throat, and lungs revealed no abnormalities. This would render these diagnoses remote possibilities. A brain tumor could be present. However, the absence of symptoms of cerebellar irritation makes this unlikely.

2. The respiratory system: Pneumonia and laryngotracheobronchitis would seem to be excluded on the basis of the absence of respiratory distress, the normal respiratory rate, and the normally clear lung fields. As mentioned previously, asphyxia does not appear to be worthy of serious consideration.

3. The cardiovascular system: At this age sudden death would, most likely, result from some congenital abnormality of the heart with subsequent embolization or congestive heart failure. Apparently this possibility is excluded by the absence of significant murmurs, cyanosis, cardiomegaly, hepatomegaly, or focal hemiplegia.

4. Severe infections: Of the severe infections which cause sudden death, one must consider the Waterhouse-Friderichsen syndrome. This is usually accompanied by a meningococcemia which is so fulminating that a complicating meningitis is frequently not an associated feature. The combination of symptoms is quite characteristic and the diagnosis readily apparent: Cyanosis, shock, hyperpyrexia, and massive purpura are typically seen. Evidently our patient did not have bilateral adrenal hemorrhages.

5. The digestive system: The presence of vomiting, dehydration, and acidosis would render this system suspect. Acidosis in itself could produce the lethargy and neurological findings. However, on closer scrutiny, one is forced not to consider this system too seriously. The commonest causes of sudden death involving the digestive system are diarrhea and malnutrition, neither of which were present in this patient. Intestinal obstruction is mentioned for the sake of completeness; but there was neither abdominal distension nor constipation. The abdomen was soft. Diabetic acidosis could be considered, but again, there is no real evidence to support this hypothesis.

6. The blood and blood forming organs: The only significant laboratory findings are a hemoglobin of 6 grams in the face of dehydration and a marked leukocytosis. In order to produce sudden death, a rapid fall in the hemoglobin must be postulated. This event could occur in one of four ways:

a. External or internal hemorrhage
b. Toxins (Lead, sulfonamides, moth balls)
c. Infections (septicemia)
d. Hemolysis (acquired or hereditary).

a. External hemorrhage obviously did not cause the sudden death of this patient. Internal hemorrhage has a large variety of etiologies, e.g., thrombocytopenia, hemophilia, hypoprothrombinemia, congenital aneurysm, brain tumor, hemangioma, subarachnoid hemorrhage, and others. None of these can be ruled out categorically. However, they do appear to be unlikely.

b. Toxic causes are eliminated probably on the basis of inadequate information and lack of a history. Chronic plumbism, however, must remain a possibility since it explains the combination of anemia and neurological symptoms.

c. Infection: Septicemia could cause rapid hemolysis, leukocytosis, and sudden death. The neurological symptoms could result from dehydration and acidosis. However, there is no clinical jaundice present, no history of a preceding infection, and no evidence of an infectious focus. This possibility cannot be eliminated on the basis of the information contained in the protocol.

d. An acquired hemolytic process appears to be unlikely. There are a number of different types of familial hemolytic anemias. Because of the race of this patient, only one of these deserves serious consideration. The most likely specific hemolytic disease would necessarily have to be sickle cell anemia with a hemolytic crisis. This diagnosis would explain the neurological findings, the gastro-intestinal symptoms, the fever, the marked leukocytosis, and the rapid reduction in the hemoglobin. In a survey of 58 children with sickle cell anemia, Conley, Martin, and Recinos[3] reported two instances of sudden death: one was a 3 year old colored boy who was dead on arrival; the other was a 12 year old colored girl admitted to the hospital in a sickle cell crisis who died 5½ hours after admission. It is apparent, then, that sickle cell anemia can cause sudden death in childhood. The anemia in our patient was probably more marked than the hemoglobin of 6 grams would indicate, since the infant was dehydrated and hemoconcentration must have been present.

In conclusion, I have selected the diagnosis of sickle cell anemia with an associated hemolytic crisis as the most likely. I have done so because it appears to be the disease which most adequately explains all of the features which were present in this patient. Since it can cause sudden death by rapid

hemolysis of red cells, I would assume that this is what happened to this infant.

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AUTOPSY FINDINGS

Enid F. Gilbert, M.D.

At autopsy the body was that of a fairly well developed and well nourished 15 month old colored female infant. The skin showed moderate dehydration. The lungs were soft and crepitant and showed no abnormalities. The weight of the heart was normal and there was a minimal degree of right ventricular dilatation.

The spleen weighed 100 grams, approximately four times the normal weight. It was dark purple and firm and on section enlarged malpighian corpuscles and prominence of the trabeculae were evident. The entire gastrointestinal tract showed marked lymphoid hyperplasia with elevation of the Peyer's patches. The mucosa of the large intestine was studded with pinpoint petechiae. There were numerous large, firm lymph nodes in the mesentery, around the hilum of the spleen, along the pancreas, and para-aortic region. Gross examination of the liver, gall bladder, adrenals, and genito-urinary tract was unremarkable. Sections of the ribs and vertebrae showed pinkish red moist trabeculated bone marrow.

On microscopic examination the lungs contained patchy areas of atelectasis and emphysema. The larger blood vessels were filled with hemolyzed blood containing sickled red blood cells. The hilar lymph nodes showed enlarged and prominent follicles. The sinusoids of the liver were dilated and filled with sickled erythrocytes. Around the portal triads were accumulations of lymphocytes with an occasional polymorphonuclear cell. The normal architecture of the spleen was distorted by hemorrhage which masked many of the malpighian corpuscles. There was marked congestion of the sinusoids with sickled red blood cells. Sections of the entire gastrointestinal tract showed marked lymphoid hyperplasia, the follicles in some areas being so numerous and hyperplastic as almost to occlude the intestinal lumen. The glomerular and interstitial capillaries were distended with sickled red blood cells. All lymph nodes showed hyperplasia of the follicles and sickled erythrocytes in the sinusoids. Sections of the bone marrow

showed marked cellularity and erythroid hyperplasia, with numerous sickled red blood cells. The remainder of the organs were unremarkable except for the generalized vascular congestion with sickled erythrocytes.

Final Pathological Diagnosis

1. Sickle cell anemia in crisis
2. Marked lymphoid hyperplasia

THE CAUSES OF DEATH DURING THE YEAR 1955; CLINICAL AND PATHOLOGICAL DIAGNOSES

E. Clarence Rice, M.D.
Grace H. Guin, M.D.

A review of the causes of death at this hospital for the year 1955 based on necropsy findings is desirable in evaluating the diagnostic ability of a medical staff and is essential in determining the results of medical and surgical treatment. Certain trends continue to be evident, viz., a reduction in the number of deaths due to infection and an increase in the proportion of deaths due to developmental anomalies.

Fewer patients are dying of infection because of the increasing number of and the effectiveness of antibiotics and chemotherapeutic agents. Infections of the central nervous system have been greatly reduced in number, but it is believed that the number is not down to an irreducible minimum. *Hemophilus influenzae* continues to be responsible for the greatest number of deaths in this category.

Deaths from congenital anomalies have shown a steady increase due to the fact that more parents are bringing their children to the hospital for the diagnosis and correction of these defects than previously. Those interested in cardiology have demonstrated their ability to diagnose diseased states correctly during life which a few years ago could only be accurately diagnosed at the autopsy table. Endocardial fibroelastosis can now be diagnosed with strong probability by the clinician. His ability to diagnose cardiovascular anomalies is truly remarkable and many excellent diagnoses have been made at this hospital, although it is somewhat surprising to note that eight patients came to necropsy with no definite diagnosis on their charts other than congenital heart disease.

Patients with congenital anomalies make up the greatest proportion of the deaths following operations as might be expected.

Deaths from malignant tumors and leukemia are more numerous than before inasmuch as the hospital continues to attract an increasing number

of patients from a larger area whose parents seek to obtain the benefits available from the improved surgical treatment and chemotherapy which is available.

Some idea of the increased effectiveness of therapy since chemotherapy and antibiotic drugs began to make their value manifest at this hospital in 1938 can be obtained from the knowledge that the annual number of deaths prior to that year exceeded 275, whereas the average number of deaths per year since 1937 has been 190. It seems quite probable that the lives of more than 1,000 infants and children at this hospital have been spared from death during the past 18 years due largely to these agents, and improved skills on the part of physicians and surgeons.

CAUSES OF DEATH DURING 1955 BASED ON CLINICAL AND PATHOLOGICAL DIAGNOSES

A Survey from January 1, 1955 through December 31, 1955

Total Hospital Deaths	141
Autopsies Performed	120
(Courtesy Autopsies)	2
Autopsy Percentage	85.1

Summary of Causes

Deaths Due to Infections	38
Deaths Due to Congenital Anomalies	30
Deaths Due to Malignant Diseases and Leukemias	16
Deaths Due to Operative Complications	9
Deaths Due to Blood Diseases	5
Deaths, Miscellaneous	22
Total	120

Clinical Diagnosis	*Pathological Diagnosis*
Infections	38 cases
Respiratory System:	16 cases
Bronchopneumonia (2)	Bronchopneumonia (2)
Malnutrition	Bronchopneumonia
Diabetes	Bronchopneumonia
Dehydration	Bronchopneumonia
Multiple congenital anomalies	Bronchopneumonia
DOA	Bronchopneumonia
Bronchiolitis	Bronchopneumonia
Congenital heart disease	Aspiration pneumonitis
DOA	Aspiration pneumonitis
Bronchopneumonia and tracheo-esophageal fistula (2)	Bronchopneumonia, tracheoesophageal fistula (2)
Empyema, staphylococcic	Empyema due to *Micrococcus pyogenes* var. *aureus*
Intracranial hemorrhage	Empyema due to *Micrococcus pyogenes* var. *aureus*; intracranial hemorrhage
Pertussis	Pertussis

Clinical Diagnosis	*Pathological Diagnosis*
Blastomycosis	Blastomycosis of lungs
Gastrointestinal Tract	7 cases
Gastroenteritis (4)	Gastroenteritis (4)
Intestinal obstruction	Enteritis
Overwhelming infection	Enteritis
Dehydration and diarrhea	Enteritis. Absence of gall bladder
Circulatory System	1 case
Bronchopneumonia	Myocarditis
Infections of the Central Nervous System	12 cases
Poliomyelitis	Poliomyelitis
Ascending paralysis	Poliomyelitis
Meningitis	Meningitis due to *E. coli*
Diarrhea	Meningitis due to *E. coli*
Meningococcemia	Meningococcal meningitis
Meningitis	Meningitis due to *H. influenzae*
Meningitis	Meningitis due to *H. influenzae*
Meningitis	Subarachnoid hemorrhage
	Subsiding meningitis due to *H. influenzae*
Meningitis and hydrocephalus	Meningitis and hydrocephalus due to coagulase negative micrococcus
Tuberculous meningitis and miliary tuberculosis (2)	Tuberculous meningitis and miliary tuberculosis (2)
Cerebral hemorrhage	Brain abscess due to *Micrococcus pyogenes* var. *aureus*
Generalized infection	2 cases
Developmental failure	Septicemia, etiology undetermined
Meningitis?	Meningococcal septicemia
CONGENITAL ANOMALIES*	30 cases
Heart	17 cases
Congenital heart disease	Atrioventricularis communis
Coarctation?	Coarctation of the aorta
	Mitral stenosis
Anomalous left coronary?	Anomalous coronary, left
Fibroelastosis?	Fibroelastosis
Congenital heart disease	Subaortic stenosis
Congenital heart disease (2)	Pulmonary stenosis (2)
Congenital heart disease	Single auricle, single ventricle
	Pulmonary stenosis
	Atrioventricularis communis
	Absent spleen
Congenital heart disease	Transposition of the great vessels
	Intraventricular septal defect
Bronchopneumonia and Mongolism	I-V and I-A septal defects
	Mongolism
Congenital heart disease (2)	Eisenmenger's complex (2)

* Two additional cases of congenital heart disease are included under operative complications.

Clinical Diagnosis	*Pathological Diagnosis*
Primary pulmonary hypertension	Eisenmenger's complex and pulmonary hypertension
Congenital heart disease	Single auricle and single ventricle
	Transposition of the great vessels
	Atrioventricularis communis
	Partial situs invertus
	Absent spleen
Tetralogy of Fallot	Transposition of the great vessels
Transposition of the great vessels	Transposition of the great vessels
Anomalous pulmonary venous return	Anomalous pulmonary venous return
Genitourinary Tract	6 cases
Left polycystic kidney	Left polycystic kidney
Right hypoplastic kidney	Right hypoplastic kidney
Congenital heart disease	Hydronephrosis, bilateral
Hypospadius	Hypospadius
Hydronephrosis	Posterior urethral valve
Urethral obstruction	Hydronephrosis, bilateral
Hydronephrosis and hydrocephalus	Hydronephrosis and hydrocephalus
Hydronephrosis and renal infection	Hydronephrosis and multiple renal abscess
Hydroureters and renal rickets	Hydroureters and renal rickets
Nervous System	7 cases
Anencephaly	Anencephaly
Biliary atresia	Hydranencephaly and hepatitis
Hydrocephalus (2)	Hydrocephalus (2)
Meningomyelocele	Meningomyelocele
Cerebral atrophy (2)	Cerebral atrophy (2)
MALIGNANT TUMORS AND LEUKEMIA	16 cases
Acute lymphocytic leukemia (8)	Acute lymphocytic leukemia (8)
Acute myelocytic leukemia	Acute myelocytic leukemia
Hodgkin's disease	Hodgkin's disease
Malignant reticuloendotheliosis	Malignant reticuloendotheliosis
Neuroblastoma	Neuroblastoma
Subdural hemorrhage	Astrocytoma
Brain tumor	Astrocytoma
Brain tumor	Medulloblastoma
Medulloblastoma	Medulloblastoma
OPERATIVE COMPLICATIONS	9 cases
I-A septal defect*	Atrioventricularis communis*
Cardiac arrest	
Hirschsprung's disease	Hirschsprung's disease
Cardiac arrest	Cardiac arrest
Intestinal atresia	Intestinal atresia
Peritonitis	Peritonitis
Diaphragmatic hernia	Diaphragmatic hernia
	Postoperative pulmonary atelectasis
Omphalocele, ileotomy	Omphalocele, postoperative
Anastomosis of ileum to the transverse colon	Anastomosis of ileum to the transverse colon

Clinical Diagnosis	*Pathological Diagnosis*
Diarrhea	Diarrhea
Biliary atresia	Peritonitis, postoperative
Laparotomy	Choledochal cyst
Duodenal obstruction	Duodenal atresia. Pulmonary atelectasis.
	Subarachnoid hemorrhage
Multiple congenital anomalies	Achrocephalosyndactyly
Decompression of temporal bone	Massive collapses and hemorrhage of the lungs
Tetralogy of Fallot*	Tetralogy of Fallot*
Pott's procedure	Acute congestion of the lungs
BLOOD DISEASE	5 cases
Anemia of undetermined origin	Anemia of undetermined origin and Septicemia due to *E. coli* and beta hemolytic streptococcus
Anemia and septicemia	Anemia and septicemia due to beta hemolytic streptococcus
Sickle cell anemia and meningitis	Sickle cell anemia and adrenal hemorrhage
Acquired hemolytic anemia and septicemia	Acquired hemolytic anemia and staphylococcic empyema
Hemophilia	Hemophilia
	Exsanguination
MISCELLANEOUS	22 cases
Fibrocystic disease of pancreas (2)	Fibrocystic disease of pancreas (2)
Meconium ileus	Meconium ileus
Adrenogenital syndrome (2)	Adrenogenital syndrome (2)
Septicemia	Hepatoadrenal necrosis
Epidermolysis bullosa	Epidermolysis bullosa
DOA	Congestive heart failure
DOA	Visceral congestion and hemorrhage
Septicemia	Visceral congestion
Mongolism	Mongolism
Transverse dislocation of the cervical vertebrae	Transverse dislocation of the cervical vertebrae
Prematurity	Prematurity
Intracranial hemorrhage (2)	Intracranial hemorrhage (2)
Massive gastrointestinal hemorrhage	Exsanguination secondary to peptic ulcer
Encephalitis	Congestion and edema of the brain
Lead encephalitis	Lead encephalitis
Acidosis	Acidosis
Hydrocephalus	Arachnoiditis
Familial dysautonomia	Familial dysautonomia
Bronchopneumonia	Bronchopneumonia
Enteritis	Cerebellar hemorrhage
Brain tumor?	Lower nephron nephrosis
Birth injury	Congestion of the brain and viscera
Congenital heart disease	Pulmonary atelectasis and hemorrhage

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*From an exhibit by Sydney H. Kane, M.D., at the American Medical Association meeting, Atlantic City, N. J., June 6-10, 1955.

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